Lilly

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October 22,1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

RE: [Docket No. 99D-2635] Lilly's response to FDA Guidance for Industry, ANDA's: In-Process Blend Uniformity Analysis

Dear Madam or Sir:

We recently received the draft guidance published by the agency titled, "ANDAs: Blend Uniformity Analysis", and were surprised both by its content and timing. It is our belief that this continues to be a very controversial topic and hence it rightly has been proposed as an early priority for PQRI research activities. Until data can be developed through the PQRI process to answer some of the significant questions which have been raised around this draft guidance we strongly believe that it would be inappropriate to reissue this guidance.

The guidance reflects the original position by the agency to which industry has provided significant objection. We continue to be very concerned about requesting the sampling of blend using technology that is known to have significant problems. The difficulties of obtaining small samples using a sampling thief from a blender have been very well established. The sampling thief tends to segregate the material resulting in a sample that is not representative of the blend. Using this technology we have observed assay results that are biased and highly variable. Industry has been using this technology for a long time during process validation, and many alternative sampling plans and statistical based approaches have been designed to address this issue (i.e. PDA technical report 25).

We also find the alternative offered by the agency to take a large sample from the blender and testing a unit dose is equally challenging. Our experience with this approach has clearly shown similar problems where the sub-sample results are clearly not representative of the original samples. We have seen results that are biased and have shown high variability as we try to sub-divide the original samples in the laboratory.

The limitations of current sampling techniques makes the proposal limits unacceptable. In addition the proposed regulation does not allow for second tier testing, therefore any failure in the blend testing will result in an automatic rejection of the finished product.

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Although this guideline is promulgated as an in-process, in reality it is an additional release requirement. We believe that this is an unnecessary burden on industry especially when we consider that the current sampling technology is not appropriate.

Given the significant difficulties with the technology for in-process blend uniformity it seems prudent to be very clear on what problem(s) the proposed additional testing is intended to address. The issue or issues are not delineated in the guidance. It is our belief that a clear indication by the agency of their concerns in this area could allow industry and the agency to develop solutions that would be more scientifically sound and practical. We continue to look for opportunities to discuss with the agency alternatives to in-process Blend testing.

For example, if the agency's general concern is to increase the assurance of the homogeneity of the final product, testing at the blender stage may not be the most appropriate approach. We know that there is a high potential for segregation and demixing of the blend as we further process the material post-testing. If assurance of uniformity of the final blend is the primary concern, discussions should be held to develop more effective approaches to better measuring final product homogeneity.

Finally we appreciate the effort the agency has put together to develop this guideline. We are looking forward to having an open discussion forum to develop alternatives to the proposed guideline. In order to make these discussions successful we need to understand what issues are driving the development of the current guidance. We thank you in advance for the attention to our comments and look forward to the opportunity to further discuss this topic.

Sincerely,

Tobias Massa Ph.D.
Director, Global Regulatory Affairs CM&C / Operations

TM:tl

cc: Eric Sheinin
Douglas Sporn
Janet Woodcock

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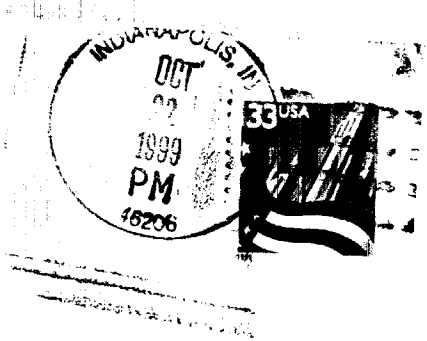

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